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TRANSMITTAL OF APPEAL BRIEF

Docket No.
CFBF-P02-002

In re Application of: Wagner et al.

Application No.	Filing Date	Examiner	Group Art Unit
08/948393	November 8, 1999	P. Gambel	1644

Invention: METHOD FOR TREATING OR INHIBITING ATHEROSCLEROSIS WITH PSGL-1

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed: May 10, 2004 .

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Dated: July 30, 2004

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Attorney Docket No. CFBF-P02-002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s):	Wagner et al.	Examiner:	P. Gambel
Serial No.:	08/948,393	Art Unit:	1644
Filing Date:	November 8, 1999		
For:	METHOD FOR TREATING AND PREVENTING ATHEROSCLEROSIS WITH PSGL-1		

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

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Patricia McKenney

Mail Stop Appeal
Commissioner for Patents
P.O. 1450
Alexandria, VA. 22313-1450
ATTENTION: Board of Patent Appeals and Interferences

Sir:

APPELLANT'S BRIEF ON APPEAL

This is an appeal to the Board of Patent Appeals and Interferences (the "Board") from the decision of the Examiner finally rejecting claims 71-73, 77-81 and 83-95, and is in furtherance of the Notice of Appeal filed on May 10, 2004, in this application. The appealed claims are as set forth in the attached Appendix. Provision for the payment of fees required for filing this brief, and any required extension of time for filing the brief, is submitted herewith. This brief is submitted in triplicate in accordance with the provisions of 37 C.F.R. §1.192(a).

REAL PARTY IN INTEREST

The real party in interest in this appeal is the CBR Institute for Biomedical Research, Inc., aka The Center for Blood Research, Inc., the assignee of the rights of the inventors in the above-identified patent application. The CBR Institute for Biomedical Research, Inc., is an affiliate of the Harvard Medical School.

RELATED APPEALS AND INTERFERENCES

There were appeals pending in related applications. However, these appeals have now been dismissed. Consequenly, there are currently no related appeals or interferences that will directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

STATUS OF CLAIMS

The status of the claims in this application is as follows. Claims 71-73, 77-81 and 83-95 are pending and are on appeal. No claims have been allowed.

STATUS OF AMENDMENTS

Claims 71-73, 77-81 and 83-95 were finally rejected in the Office Action of February 10, 2004. An Amendment After Final Rejection was filed on May 5, 2004. No Advisory Action has been received from the US Patent and Trademark Office advising appellants as to whether the Amendment has been entered. For purposes of this appeal, however, appellants assume that this amendment would be entered. Accordingly, the appended claims incorporate the most recent claim amendments.

SUMMARY OF INVENTION

Atherosclerosis, a principal cause of heart attacks among adults in the United States, results from the restricted flow of arterial blood due to the accumulation of fibrous plaque over time in the arterial lumen. Death or incapacitation of the subject may result from the rupture of the fibrous cap of the plaque, causing hemorrhage, thrombosis and occlusion of the artery. The fibrous plaque is formed from fatty streaks which develop into lesions composed predominantly of layers of smooth muscle cells, lipid-filled macrophages and T cells. The earliest stages of atherosclerosis occur when migrating monocytes and T lymphocytes bind to the lumen of the arterial wall. Atherosclerosis is a chronic, ling term condition, as distinguished from more acute conditions such as local inflammation. Page 1, line 17 to page 2, line 22. Appellants have found that P-selectin is implicated in the origins of atherosclerosis as a result of the mediation of platelet or endothelial cell binding and adhesion to monocytes. Page 5.

In one embodiment, the claimed invention relates to a method for treating or inhibiting atherosclerosis in a mammal, or for decreasing the formation or growth of atherosclerotic lesions in a mammal, by the administration of an effective amount of P-selectin glycoprotein ligand-1 ("PSGL-1"), including soluble forms, fragments, synthetic analogs and mimetics of PSGL-1. The PSGL-1 inhibits the interaction of P-selectin and a ligand of P-selectin. The PSGL-1 may additionally be capable of inhibiting the interaction between E-selectin and a ligand of E-selectin. Page 7, lines 30-34, and page 12, lines 21-26.

In another embodiment, the claimed invention relates to methods for decreasing the formation or growth of atherosclerotic lesions in a mammal by the administration of an effective amount of P-selectin glycoprotein ligand-1 ("PSGL-1"), soluble forms of PSGL-1, PSGL-1 fragments, and synthetic analogs and mimetics of PSGL-1, prior to, or in conjunction with, a vessel-corrective technique. The vessel corrective technique can be angioplasty, a stenting procedure, atherectomy or bypass surgery, and the P-selectin can be administered sequentially over an extended period of time. Page 14, lines 20-30.

In a further embodiment, the claimed invention relates to methods for treating restenosis in a mammal by performing a vessel corrective technique on the mammal, and subsequently

administering to the mammal an effective amount of PSGL-1, soluble forms of PSGL-1, PSGL-1 fragments, and synthetic analogs and mimetics of PSGL-1, after performing the vessel corrective technique. The vessel corrective technique is angioplasty, stenting procedure, atherectomy, and bypass surgery. Page 14.

ISSUES

The issues to be decided in this appeal is as follows:

1. Whether claims 71-73, 77-81 and 83-95 are unpatentable under 35 U.S.C. 102(e) as being anticipated by the Cummings et al. reference (U.S. Patent No. 5,464,778).

2. Whether claims 71-73, 77-81 and 83-90 are unpatentable under 35 U.S.C. 103(a) as obvious over the Cummings et al. reference (U.S. Patent No. 5,464,778) in view of the Larsen et al. reference (U.S. Patent No. 5,840,679).

3. Whether claims 71-73, 77-81 and 83-90 are obvious under the judicially created doctrine of obviousness-type double patenting in view of claims 40-41, 45, 49-52, 56, 59-60 and 73-74 of co-pending application Serial No. 09/436,076, and claims 39-88 of co-pending application Serial No. 09/863,642.

GROUPING OF CLAIMS

Claims 71, 90, 91 and 95 are independent claims. Claims 72, 73, 77-81 and 83-89 are dependent on independent claim 71, and stand or fall with this claim. Claims 92-94 are dependent on independent claim 91, and stand or fall with claim 91. Claim 71 differs from claim 90 in that claim 90 requires that the P-selectin inhibitor inhibits the interaction of P-selectin and a ligand of P-selectin. Claim 71 also requires, in addition, that the P-selectin inhibitor inhibits the interaction of E-selectin and a ligand of E-selectin. Therefore, clams 71 and 90 do not stand or

fall together. Independent claims 91 and 95 require the use of a surgical procedure. Accordingly, claims 91-95 do not stand or fall with the remaining claims. Furthermore, to the extent that claims 95 relates to the treatment of restenosis, this claim does not stand or fall with claims 91-94.

ARGUMENT

I. Rejection of Claims 71-73, 77-81 and 83-90 under 35 U.S.C. 102(e)

Claims 71-73, 77-81 and 83-90 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Cummings et al. (U.S. Patent No. 5,464,778). Appellants respectfully request reversal of this rejection by the Board.

The Cummings et al. reference states that the glycoprotein ligand for P-selectin, or antibodies or fragments thereof, can be used as inhibitors of P-selectin binding to cells. The Cummings et al. patent discusses atherosclerosis in a section of the patent labeled "Clinical Applications", at col. 18, line 33 of the patent. In particular, the patent states that atherosclerosis is an example of a pathological situation in which an inflammatory response may occur, and the glycoprotein ligand can be used to treat such an inflammatory response. See col. 18, lines 34-53.

As noted above, atherosclerosis is not an inflammatory or acute condition, but a long term chronic condition resulting from the accumulation of plaque in the arteries. While there may be short term inflammatory consequences of atherosclerosis, these are merely acute symptoms underlying the chronic nature of the disease. Rather than describing the treatment of the underlying disease of atherosclerosis, the reference simply teaches the treatment of potentially inflammatory conditions that may result from atherosclerosis. See col. 18, lines 54-62, as well as col. 19, line 64-col. 20, line 5, of the reference, which states that the glycoprotein ligand can be used to treat inflammatory conditions, such as thrombus formation and ischemia, resulting from the rupture of a fully developed atherosclerotic plaque. This teaching is directed to treating the effects of the disease, rather than the treatment of the disease itself. Since

atherosclerosis is a long term condition, any treatment of the disease necessarily requires a long term treatment program which is not disclosed in the reference.

In contrast to Cummings et al., the present invention is directed to the treatment of atherosclerosis by decreasing the formation or growth of atherosclerotic lesions. This treatment requires the long term administration of a drug for treating a chronic build up of lesions and plaque in arteries. The Cummings et al. reference does not mention the use of p-selectin glycoprotein ligand to decrease the formation or growth of atherosclerotic lesions, but addresses the possible effects of atherosclerotic plaque rupture as noted previously.

Appellants also maintain that the declaration filed in this application under 37 CFR 1.131 (the "Wagner declaration") is effective in overcoming the Cummings et al. reference by antedating that reference. The Wagner declaration demonstrates that the present invention was conceived prior to the effective date of the Cummings et al. reference, and diligently reduced to practice thereafter. Consequently, it is appellants' position that the Cummings et al. primary reference has been effectively antedated, and is therefore not prior art.

Specifically, the Wagner declaration demonstrates that, prior to the effective date of the reference (the earliest filing date), appellants discovered that the binding of P-selectin and a ligand of P-selectin contributed to the development of atherosclerosis lesions. As a result of that discovery, appellants deduced that inhibitors of P-selectin can be used to treat atherosclerosis in mammals based on the role of P-selectin and/or E-selectin on the pathogenesis of atherosclerosis as claimed in the present application.

The Examiner states that the Wagner declaration fails to establish that appellants had possession of the invention recited in the claims. Appellants maintain that the original claims covered a genus of agents which could be used to practice the invention, and the genus included several species including PSGL-1. The original claims were limited by the Examiner to particular species of the genus as a result of an election of species and/or restriction requirement. Notwithstanding, appellants' position remains that possession of the genus is sufficient to constitute possession of the species. The alternative result would require appellants to demonstrate possession of each and every species delineated in the restriction requirement and this is unrealistic and contrary to the case law. See *In re Schaub*, 190 USPQ 324 (CCPA 1976).

The Examiner has also attacked the sufficiency of the Wagner declaration based on the following alleged shortcomings. The declaration states that the development of the knockout mouse model used in the reduction to practice occurred during the time period from November 16, 1992 to September 13, 1993, although appellants' experimental results were collected and analyzed on or about May 6, 1994. This represents a time period of some eight (8) months which is presumably viewed as excessive. Moreover, the declaration utilizes a knockout mouse model to simulate a deficiency of P-selectin, rather than a specific inhibitor of P-selectin and ligand binding, such as P-selectin glycoprotein ligand.

With regard to the question of diligence regarding the reduction to practice of the invention, the Wagner declaration (paragraphs 7 and 8) states that it took 8 months following the preparation of the mice for the mice to develop atherosclerosis due to the fact that the mice are resistant to atherosclerosis. The fact that it took 8 months for the mice to develop atherosclerosis is not unreasonable or unusual in light of this natural resistance to the formation of atherosclerosis plaque. Overcoming this resistance is a time consuming undertaking, involving feeding the mice a high lipid diet for a prolonged period of time. Since atherosclerosis is a long term, chronic condition, it is not unusual that it look the mice 8 months to develop symptoms of the disease. Note that the mice were fed a high lipid diet promptly after their genetic makeup was confirmed, and the mice were then sacrificed immediately thereafter. Thus, the work described in the Wagner declaration was undertaken diligently and expeditiously, even though the science necessarily imposes constraints on the speed with which the work could have been completed due to the inherent limitations of the mouse model as described.

The Examiner has relied upon the Cummings et al. reference as disclosing the use of P-selectin glycoprotein ligand for the treatment of atherosclerosis. Although appellants disagree with the Examiner's characterization of Cummings et al., for purposes of the sufficiency of the Wagner et al. declaration, appellants assume this characterization of the reference is accurate. Appellants believe that a fair reading of the Wagner declaration demonstrates the conception of the invention as claimed by appellants and as described in the reference prior to 1988, the effective date of the reference, followed by a diligent reduction to practice thereafter.

The Wagner declaration utilizes a knockout mouse model deficient in P-selectin to establish the principal that a reduction in P-selectin level correlates with a reduction in the accumulation of atherosclerotic lesions and plaque, and a commensurate reduction in atherosclerosis. The use of the knockout mouse model is intended by the inventors to simulate the activity of an inhibitor of P-selectin and ligand binding, and is so stated in the declaration. Appellants submit that one skilled in this art would recognize that this is a standard approach to simulating the activity of an inhibitor over a long period of time, and would be recognized as such. The Board will appreciate the practical difficulties in the science involved in the invention, and that a method for preventing atherosclerosis, a long term, chronic condition, would be inherently difficult to reduce to practice. However, these difficulties should not preclude appellants from obtaining the fruits of their labor. It is noted, for instance, that the broad scope of the invention as originally claimed was not limited to particular inhibitors, and that the more limited claim scope now before the Board is the result of a restriction requirement imposed by the Examiner. Notwithstanding, the showing made in the declaration is generic to both the invention now claimed and the reference, and is adequate to antedate the reference.

II. Rejection of Claims 71-73, 77-81 and 83-90 under 35 U.S.C. 103(a)

Claims 71-73, 77-81 and 83-90 have also been rejected under 35 U.S.C. §103(a) as being obvious over Cummings et al. (U.S. Patent No. 5,464,778) in view of Larsen et al. (U.S. Patent No. 5,840,679). Appellants respectfully request reversal of this rejection by the Board.

The Cummings et al. reference has been discussed in detail above. The Larsen et al. reference has apparently been cited as disclosing the use of P-selectin ligand glycoprotein in combination with other therapeutic agents for the treatment of various inflammatory conditions. However, Larsen et al., like Cummings et al., does not relate to the treatment of chronic conditions, such as atherosclerosis, but is instead directed to the treatment of inflammatory or acute conditions.

Moreover, neither Cummings et al. nor Larsen et al. disclose that a treatment for atherosclerosis can be administered or in conjunction with a vessel-corrective technique, as

recited in applicant's claims 91-95. Claims 91-95 require the use of surgical procedures. With regard to restenosis (claim 95) and atherosclerosis (claims 91-94), appellants also maintain that these conditions are art recognized as different medical disorders: restenosis refers to a renarrowing or blockage of an artery at the site where a surgical procedure, such as angioplasty or a stent procedure, has already occurred; whereas atherosclerosis is a chronic, long term narrowing of blood vessels due to an accumulation of plaque in the arteries.

The Examiner has criticized the Wagner declaration as not being commensurate in scope with the scope of the appealed claims. In particular, the Examiner states that since the Wagner declaration fails to disclose a vessel corrective technique, or a method for treating restenosis, it is not commensurate with the scope of the claims. In this regard, the Examiner has taken the position that the Wagner declaration must establish possession of either the whole invention as claimed, or a subset of the invention falling within the scope of the claims, citing *In re Tanczyn,* 146 USPQ 298 (CCPA 1976), and MPEP 715.02. Appellants respectfully disagree with this conclusion as applied to the facts of this appeal.

Appellants' position is that it is only necessary for the declaration to disclose all of the essential features of the reference being antedated. In this regard, see MPEP 515.02 which provides, in part, that where the differences between the claimed invention and the disclosure in the reference renders the claimed invention obvious, the declaration antedating the reference is required to show no more than what the reference shows. See also *In re Stryker*, 435 F.2d 1340, 168 USPQ 372 (CCPA 1971).

III. Rejection of Claims 71-73, 77-81 and 83-95 under 35 U.S.C. 103(a)

Claims 71-73, 77-81 and 83-95 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting, on the basis of claims 40-41, 45, 49-52, 56, 59-60 and 73-74 of co-pending application Serial no. 09/436,076, and claims 39-88 of co-pending application Serial no. 09/863,642.

Regardless of the merits of this rejection, appellants are prepared to file a terminal disclaimer to obviate the obviousness-type double patenting rejection should the Board reverse the remaining rejections in this appeal.

CONCLUSION

Claims 71-73, 77-81 and 83-95 are deemed to be patentable over Cummings et al., either alone or in combination with Larsen et al. for the reasons discussed above. Moreover, appellants submit that a fair and objective reading of the Wagner declaration would lead to the conclusion that the Cummings et al. primary reference has been effectively antedated and removed as a basis for rejecting the appealed claims. Further, appellants maintain that the references fail to teach a method for preventing the growth or formation of atherosclerotic lesions in a mammal in combination with a surgical technique as recited in appended claims 91-94 and 95.

Accordingly, for the reasons presented in this brief, appellants respectfully urge the Board to reverse the rejections made in the final Office Action, and to allow all of the appended claims.

Appellants hereby authorize the Commissioner, to debit the $330.00 fee for filing this appeal brief from Appellant's Deposit Account No. 18-1945. If there are any other fees not accounted for above, Appellants hereby authorize the Commissioner to charge the fee to Deposit Account 18-1945.

Respectfully submitted,

ROPES & GRAY

Date: 7/30/04

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APPENDIX

71. A method for treating or inhibiting atherosclerosis in a mammal by decreasing the formation or growth of atherosclerotic lesions comprising:

providing an agent for inhibiting an interaction between P-selectin and a ligand of P-selectin and between E-selectin and a ligand of E-selectin; and

administering said agent to a mammal in need of such treatment so as to cause such inhibition to occur, wherein said agent is selected from the group consisting of PSGL-1, soluble forms of PSGL-1, fragments of PSGL-1, and synthetic analogs or mimetics of PSGL-1, said agent being effective to inhibit the interaction between P-selectin and a ligand of P-selectin and between E-selectin and a ligand of E-selectin.

72. The method of claim 71 wherein said P-selectin is on a cell.

73. The method of claim 72 wherein said cell is an endothelial cell.

77. The method of claim 71 wherein said PSGL-1 is on a cell, selected from the group consisting of monocytes, neutrophils, eosinophils, CD+4 T cells, CD+8 T cells, and natural killer cells.

78. The method of claim 71 wherein the PSGL-1 is on a leukocyte.

79. The method of claim 78 wherein said leukocyte is a neutrophil.

80. The method of claim 78 where said leukocyte is a monocyte.

81. The method of claim 71 wherein said P-selectin can bind to said PSGL-1 in the absence of said agent.

83. The method of claim 71 wherein said agent is administered in sequential exposures over a period of hours, days, weeks, months or years.

84. The method of claim 71 wherein said agent is administered repeatedly, or by a controlled release delivery system.

85. The method of claim 71 wherein said agent is administered in combination with other therapeutic agents.

86. The method of claim 72 wherein said cell is a platelet.

87. The method of claim 71 wherein said mammal is human.

88. The method of claim 71 wherein said agent is administered in a dose of from about 0.01 mg/kg to about 200mg/kg of body weight.

89. The method of claim 71 wherein said agent is administered at a dose of about 100 mg/kg of body weight.

90. A method for treating or inhibiting atherosclerosis in a mammal by decreasing the formation or growth of atherosclerotic lesions comprising:

providing an agent for inhibiting an interaction between P-selectin and a ligand of P-selectin; and

administering said agent to a mammal in need of such treatment so as to cause such inhibition to occur, wherein said agent is selected from the group consisting of PSGL-1, soluble forms of PSGL-1, fragments of PSGL-1, and synthetic analogs or mimetics of PSGL-1, said agent being effective to inhibit the interaction between P-selectin and a ligand of P-selectin.

91. A method for decreasing the formation or growth of atherosclerotic lesions in a mammal comprising:

providing an agent for inhibiting an interaction between P-selectin and a ligand of P-selectin; and

administering an effective amount of said agent to a mammal in need of such treatment so as to cause such inhibition to occur, wherein said agent is selected from the group consisting of PSGL-1, soluble forms of PSGL-1, fragments of PSGL-1, and synthetic analogs or mimetics of PSGL-1, wherein said agent is administered prior to, or in conjunction with, a vessel-corrective technique.

92. The method of claim 91, wherein said vessel-corrective technique is selected from the group consisting of angioplasty, stenting procedure, atherectomy, and bypass surgery.

93. The method of claim 91, wherein said agent is administered in sequential exposures over a period of hours, days, weeks, months or years.

94. The method of claim 91, wherein said agent is administered in combination with other therapeutic agents.

95. A method for treating restenosis in a mammal to which a vessel-corrective technique is administered comprising:

performing a vessel-corrective technique selected form the group consisting of angioplasty, stenting procedure, atherectomy, and bypass surgery on a mammal; and

administering to said mammal, after said vessel-corrective technique, an effective amount of an agent selected from the group consisting of PSGL-1, soluble forms of PSGL-1, fragments of PSGL-1, and synthetic analogs or mimetics of PSGL-1, such that the restenosis occurring after said vessel-corrective technique is thereby treated.